

I. AMENDMENTS

Amendments to the Claims:

This listing of claims will replace all prior versions, and listings, of claims in the application:

Listing of Claims:

1. (Currently Amended) A method of ~~regulating cytotrophoblast differentiation and migration inhibiting proteolytic conversion of inactive TGF-β to active TGF-β by a cation independent mannose-6-phosphate (CIM6P) receptor expressed on a cytotrophoblast cell, the method comprising regulating the competition for binding to the cation independent mannose-6-phosphate (CIM6P) receptor between IGF-II and latent TGF-β by administration of administering~~ a differentiation factor selected from the group consisting of IGF-II, an ~~IGF-II analogue, a precursor of IGF-II, an isomer of IGF-II and an analog of IGF-II and an antibody specific against latent TGF-β to thereby promote the interaction between said IGF-II and in an amount sufficient to promote binding of said differentiation factor to said CIM6P receptor and thereby inhibit proteolytic conversion of inactive TGF-β to active TGF-β by said receptor.~~

2. (Currently amended) [[A]] ~~The method of Claim 1, wherein said administration of said differentiation factor inhibits said cytotrophoblast cell from differentiating from a migratory or invasive cell type to a non-migratory or non-invasive cell type promoting the implantation of an embryo in the uterine decidua endometrium, the method comprising regulating the competition for binding to the cation independent mannose-6-phosphate (CIM6P) receptor between IGF-II and latent TGF-β by administration of a differentiation factor selected from the group consisting of IGF-II, an IGF-II analogue and an antibody specific against latent TGF-β to thereby promote the interaction between said IGF-II and said CIM6P.~~

3. (Currently Amended) The method of ~~claim 2~~ Claim 1, wherein said differentiation factor is administered to an embryo produced by in vitro fertilization for implantation into a female mammal.

4. (Currently Amended) The method of ~~claim 2~~ Claim 1, wherein said differentiation factor is administered to a pregnant female subject in need thereof mammal so as to inhibit proteolytic conversion of inactive TGF-β to active TGF-β by said cytotrophoblast cells in said female mammal.

5. (Currently Amended) The method of ~~claim 2~~ Claim 4, wherein said differentiation factor is administered to [[a]] said pregnant female subject mammal in the first half of pregnancy.

6. (Currently Amended) The method of ~~claim 2~~ Claim 4, wherein said differentiation factor is administered to ~~an embryo while maintaining said embryo in a relatively hypoxic environment~~ said female mammal to improve a characteristic selected from the group consisting of placental growth, placental development and placental differentiation in said female mammal.

7. (Currently amended) The method of ~~claim 2~~ Claim 4, wherein said female mammal is embryo comprises a mammalian embryo selected from the group consisting of a human, a horse, a cow, a pig, a goat and a sheep.

8. (Withdrawn) A method of preventing the implantation of an embryo in the uterine decidual endometrium, the method comprising regulating the competition for binding to the cation independent mannose-6-phosphate (CIM6P) receptor between IGF-II and latent TGF- β by administration of a differentiation factor selected from the group consisting of latent TGF- β , a TGF- β analogue and an antibody specific against IGF-II that inhibit the interaction between IGF-II and CIM6P.

9. (Withdrawn) A method of regulating differentiation and migration of embryonic stem cells or adult stem cells, the method comprising regulating the competition for binding to the cation independent mannose-6-phosphate (CIM6P) receptor between IGF-II and latent TGF- β by administration of an differentiation factor selected from the group consisting of IGF-II, an IGF-II analogue and an antibody specific against latent TGF- β that promote the interaction between IGF-II and CIM6P.

10. (Withdrawn) A method of promoting terminal differentiation of embryonic stem cells or adult stem cells, the method comprising regulating the competition for binding to the cation independent mannose-6-phosphate (CIM6P) receptor between IGF-II and latent TGF- β and exposing said cells to reduced levels of IGF-II, whereby the stem cell CIM6P receptors are able to bind latent TGF- β and thereby promote the activation of TGF- β .

11. (Withdrawn) A method of promoting stem cell division and stem cell migration, the method comprising regulating the competition for binding to the cation independent mannose-6-phosphate (CIM6P) receptor between IGF-II and latent TGF- β and exposing said cells to

increased levels of IGF-II, whereby the stem cell CIM6P receptors are unable to bind latent TGF- β and thereby inhibiting the activation of TGF- β .

12. (Withdrawn) A method of diagnosing a predisposition of cytotrophoblast cells or stem cells to differentiate and migrate, the method comprising determining in a mother, father or an embryo the presence of a polymorphic form of a gene wherein the level of expression of said gene serves to regulate the competition for binding to the cation independent mannose-6-phosphate (CIM6P) receptor between IGF-II and latent TGF- β and, whereby the CIM6P receptors have altered ability to bind latent TGF- β and thereby altered ability to activate TGF- β .

13. (Withdrawn) The method of claim 12, wherein said gene is selected from the group consisting of an insulin-like growth factor II gene, a urokinase plasminogen activator gene, a urokinase plasminogen activator receptor gene, a CIM6P (type-2 IGF) receptor gene, a TGF- β gene, a plasminogen gene and any polymorphic forms thereof.

14. (Withdrawn) A method of diagnosing a predisposition of cytotrophoblast cells to differentiate and migrate, the method comprising determining in a mother, father or embryo the sequence of nucleotides in the DNA near the insulin-like growth factor II gene to thereby determine the capacity of the cytotrophoblast to migrate into the uterine decidua and the capacity of the placenta to transport substrates to the embryo, said insulin-like growth factor II gene comprising the insulin (INS) variable number of tandem repeats (VNTR).

15. (Withdrawn) A method of determining the ability of cytotrophoblast cells to differentiate and migrate, the method comprising measuring the amount of messenger RNA transcribed from the insulin-like growth factor II gene in an embryo.

16. (Withdrawn) A method of determining the ability of cytotrophoblast cells to differentiate and migrate, the method comprising measuring the amount of insulin-like growth factor II protein secreted by a mammalian embryo.

17. (Withdrawn) A method of determining the ability of cytotrophoblast cells to differentiate and migrate, the method comprising measuring the amount of insulin-like growth factor II protein circulating in maternal and paternal blood.

18. (New) The method of Claim 4, wherein said differentiation factor is administered to said female mammal by a device selected from the group consisting of a subcutaneous delivery device and a vaginal pessary.

19. (New) The method of Claim 4, wherein administration of said differentiation factor to said female mammal promotes a result selected from the group consisting of implantation and migratory behavior of an embryo into the uterine endometrium in said female mammal.

20. (New) The method of Claim 4, wherein administration of said differentiation factor to said female mammal is used to minimize a condition selected from the group consisting of infertility, implantation failure, miscarriage, recurrent spontaneous miscarriage, pre-eclampsia, and placental abruption in said female mammal.

21. (New) The method of Claim 3, wherein administration of said differentiation factor to said embryo promotes a result selected from the group consisting of implantation and migratory behavior of an embryo into the uterine endometrium in said female mammal.

22. (New) The method of Claim 3, wherein administration of said differentiation factor to said embryo is used to minimize a condition selected from the group consisting of infertility, implantation failure, miscarriage, recurrent spontaneous miscarriage, pre-eclampsia, and placental abruption in said female mammal.

23. (New) The method of Claim 3, wherein said differentiation factor is administered to said embryo to improve a characteristic selected from the group consisting of placental growth, placental development and placental differentiation in said female mammal.

24. (New) A method of improving a characteristic selected from the group consisting of placental growth, placental development and placental differentiation in a pregnant female mammal, the method comprising administering to a pregnant female mammal an effective amount of a differentiation factor selected from the group consisting of IGF-II, a precursor of IGF-II, an isomer of IGF-II and an analog of IGF-II.

25. (New) A method of promoting implantation of an embryo into the uterine endometrium in a female mammal, the method comprising administering to said female mammal an effective amount of a differentiation factor selected from the group consisting of IGF-II, a precursor of IGF-II, an isomer of IGF-II and an analog of IGF-II.

26. (New) A method of minimizing a condition selected from the group consisting of implantation failure, miscarriage, recurrent spontaneous miscarriage, pre-eclampsia, and placental abruption in a female mammal, the method comprising administering to said female mammal an effective amount of a differentiation factor selected from the group consisting of IGF-II, a precursor of JGF-II, an isomer of IGF-II, and an analog of IGF-II.

27. (New) A method of improving a characteristic selected from the group consisting of placental growth, placental development and placental differentiation in a female mammal, the method comprising administering to an embryo produced by in vitro fertilization for implantation into said female mammal an effective amount of a differentiation factor selected from the group consisting of IGF-II, a precursor of IGF-II, an isomer of IGF-II, and an analog of IGF-II.

28. (New) A method of promoting implantation of an embryo into the uterine endometrium of a female mammal, the method comprising administering to an embryo produced by in vitro fertilization for implantation into said female mammal an effective amount of a differentiation factor selected from the group consisting of IGF-II, a precursor of IGF-II, an isomer of IGF-II and an analog of IGF-II.

29. (New) A method of minimizing a condition selected from the group consisting of implantation failure, miscarriage, recurrent spontaneous miscarriage, pre-eclampsia, and placental abruption in a female mammal, the method comprising administering to an embryo produced by in vitro fertilization for implantation into said female mammal an effective amount of a differentiation factor selected from the group consisting of IGF-II, a precursor of IGF-II, an isomer of IGF-II and an analog of IGF-II.